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MECHANISMS OF ATRIAL FIBRILLATION IN COVID-19

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Atrial fibrillation (AF) is the most frequent form of cardiac arrhythmia in COVID-19 infected patients. The occurrence of AF paroxysms is often associated with the acute period of infection in time. At the same time, the pathophysiological mechanisms of the occurrence of AF associated with COVID-19 remain insufficiently studied. The review considers the available literature data on the influence of factors such as reduced availability of angiotensin-converting enzyme 2 receptors, interaction of the virus with the cluster of differentiation 147 and sialic acid, increased inflammatory signaling, "cytokine storm", direct viral damage to the endothelium, electrolyte and acid-alkaline balance in the acute phase of severe illness and increased sympathetic activity.

Key words: atrial fibrillation; COVID-19; angiotensin-converting enzyme 2 receptor; myocardial fibrosis; myocardial remodeling; cytokine storm

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Since the outbreak of the novel coronavirus infection (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) strain, a large amount of data has emerged on the epidemiological link between cardiovascular disease and COVID-19. In patients with COVID-19, one of the frequent complications is arrhythmias, the most common form of which is atrial fibrillation (AF). Although electrical instability, calcium metabolism, and structural remodeling play a key role in the pathophysiology of AF, its exact causes and mechanisms remain unclear in most patients with COVID-19 [1].

The purpose of our review is to consider possible pathological and immunological mechanisms for the occurrence of AF in COVID-19.

EPIDEMIOLOGY OF COVID-19 ASSOCIATED WITH ATRIAL FIBRILLATION

COVID-19 infection is an acute illness with an incubation period averaging five to six days, in some cases up to 14 days [2]. This relatively short period of time is not enough for the development of fibrosis, which would serve as a substrate for the development of AF [3]. However, the occurrence of paroxysmal AF is often time-related precisely with the acute period of infection. In a study including 414 patients with COVID-19, newly diagnosed AF was reported in 12.1% of hospitalized patients [4]. In patients who required hospitalization in intensive care units, the incidence of newly registered AF reached 27.5% [5].

A number of other studies have demonstrated that patients with COVID-19 who developed AF were older, and most of them had at least one pre-existing risk factor, including arterial hypertension [6, 7]. Older age and the presence of heart failure were also associated with a greater likelihood of AF during the acute period of COVID-19 [8, 9]. It should be noted that the presence of AF in the acute period had a significant impact on the prognosis. The onset of AF is considered as an independent predictor of embolic events in patients with COVID-19 [10]. In addition, the occurrence of AF was associated with a higher risk of developing ventricular arrhythmias [4].

Thus, COVID-19 patients with new-onset AF may have a pre-existing substrate for AF, and acute COVID-19 infection may serve as a trigger for initiation of AF, consistent with a temporal association between new-onset AF and COVID-19 [11].

The pathophysiology of AF associated with COVID-19 is not well understood. Proposed mechanisms include reduced availability of angiotensin-converting enzyme 2 (ACE2) receptors, interaction of cluster of differentiation 147 (CD147) and proteins with sialic acid, enhanced inflammatory signaling, inflammatory cytokine storm, direct viral damage to the endothelium, electrolyte and acid-base balance disorders in the acute phase of a severe illness, and imbalance of the autonomic nervous system [12] (Fig. 1).

ANGIOTENSIN CONVERTING ENZYME

ACE2 is a transmembrane receptor with an extracellular N-glycosylated N-terminal region containing a carboxypeptidase site, as well as a short intracellular C-terminal cytoplasmic tail. The N-terminal peptidase domain is the site of ACE2 binding to SARS-CoV [13]. Although other receptors on the surface of human cells, such as sialic acid [14] and an inducer of extracellular matrix metallo-

proteinase inducer (CD147) [15], have also been shown to mediate entry of SARS-CoV-2 into the cell, ACE2 is likely to be the main entry pathway. SARS-CoV-2, through its surface spike glycoprotein, interacts with ACE2 and enters host cells such as pneumocytes, macrophages, endothelial cells, pericytes, and cardiomyocytes. Pericytes surround the endothelium in the microvasculature and are involved in maintaining the integrity of microvessels, providing structural stabilization of the vasculature and preventing vascular permeability [16]. If the microvascular circulation is damaged, this can lead to further inflammation, cardiac fibrosis, and thrombosis [17].

SARS-CoV-2 infection can disrupt the interaction between pericytes and endothelium and cause an increase in vascular permeability. If this happens, the pericytes or endothelial cells begin to release a number of growth factors that attempt to restore the integrity of the microvessels. Pericytes have been shown to release mediators such as vascular endothelial growth factor, basic fibroblast growth factor, heparin-binding epidermal growth factor, keratinocyte growth factor, transforming growth factor-β1 (TGF-β1), platelet growth factor, thrombopoietin, angiopoietin 1 , angiopoietin 2 (Ang2), hepatocyte growth factor, stem cell factor, factor-1 alpha, etc. [18]. Some of these factors are associated with AF, such as Ang2 [19], TGF-β1 [20], microRNA-132 [21], and hepatocyte growth factor [22]. These factors also promote local tissue inflammation by disrupting atrial cellular electrophysiology, either directly or through structural changes in the entire atrium and/or cell matrix [23].

ACE2 plays an important regulatory role in the renin-angiotensin system due to its ability to convert the potent vasoconstrictor angiotensin II (AngII) into the vasodilatory peptide angiotensin-1-7 (Ang1-7). After binding to SARS-CoV-2, ACE2 expression on the cell surface decreases due to internalization, which leads to suppression of the key pathway of AngII degradation to Ang1-7. An increase in the AngII:Ang1-7 ratio contributes to the development of myocardial hypertrophy, vasoconstriction, tissue fibrosis, and oxidative stress, potentially increasing susceptibility to AF [24].

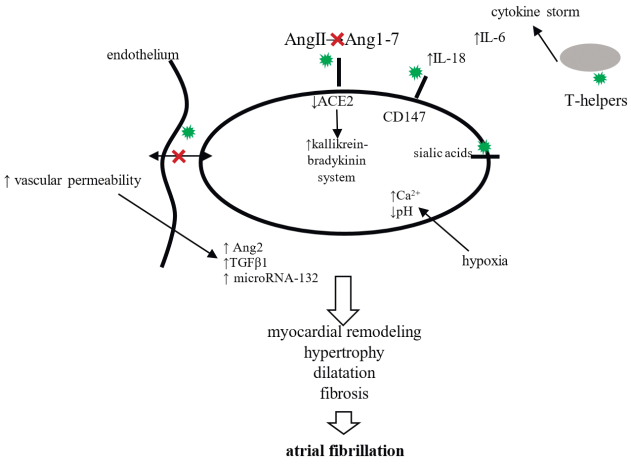

Fig. 1. Proposed mechanisms of atrial fibrillation in patients with COVID-19. Note: ACE2 - angiotensin-converting enzyme 2, AngII - angiotensin II, Ang1-7 - angiotensin 1-7, Ang2 - angiopoietin 2, IL - interleukin, TGF-β1 - transforming factor β1.

In addition, a decrease in ACE2 expression in the vasculature can induce activation of the kallikrein-bradykinin system, thereby increasing vascular permeability, promoting endothelial dysfunction and inflammation, and exacerbating existing atherosclerosis and diabetes, two common risk factors for AF [25]. It should be noted that a decrease in ACE2 expression predisposes to the development of inflammation of epicardial adipose tissue, pericarditis, and the development of pericardial effusion, and each of these factors can contribute to the onset of AF [26-27].

BASIGIN

One of the possible pathogenetic mechanisms for the occurrence of COVID-19 AF is basigin (CD147), a transmembrane glycoprotein belonging to the class of immunoglobulins and playing a functional role in facilitating the invasion of SARS-CoV-2 into host cells, including cardiomyocytes [28]. Experimental studies have shown that CD147 is a powerful inducer of interleukin-18 (IL-18) mRNA expression in cardiomyocytes. IL-18 activates metalloproteinases and increases the degradation of extracellular matrix components, causing heart remodeling [29]. A number of studies have shown that the level of circulating IL-18 positively correlates with the development of AF [30, 31].

SIALIC ACIDS

Spike proteins of coronaviruses are able to bind to sialic acids present on the cell surface. One of these proteins is N-acetylneuraminic acid, which plays an important role in the development of coronary artery diseases and activation of fibrosis processes in the myocardium. Thus, N-acetylneuraminic acid can contribute to the onset of AF [32].

CYTOKINE STORM

An additional explanation for the occurrence of AF in COVID-19 is the activation of the immune system. SARS-CoV-2 infection is manifested by the development of a systemic inflammatory response and hyperactivation of immune cells, which leads to the emergence of a “cytokine storm” caused by an increased level of cytokines as a result of an imbalance between T-helper-1 and T-helper-2 cells [33]. Excessive release of proinflammatory cytokines can lead to apoptosis or necrosis of myocardial cells, which can impair intraatrial repolarization and conduction. Some cytokines, such as interleukin-6 (IL-6), have direct pro-atherogenic effects, including stimulation of vascular smooth muscle proliferation, endothelial cell activation, and platelet activation. It should be noted that in a state of hyperinflammatory response, coronary atherosclerotic plaques are prone to rupture, causing acute myocardial injury and increasing susceptibility to arrhythmias [34].

ELECTROLYTE DISORDERS

More than half of hospitalized patients with COVID-19 have hypokalemia. This is probably due to an increased loss of potassium in the urine due to a decrease in the effect of ACE2 on the renin-AngII system, which leads to an increase in sodium and water reabsorption, an increase in blood pressure and potassium excretion. In ad-

dition, patients with COVID-19 often experience gastrointestinal symptoms, such as diarrhea and vomiting, which reduce the body's potassium stores [35, 36]. Subsequently, hypokalemia leads to cellular hyperpolarity, increased resting membrane potential, and accelerated depolarization in heart cells, which predisposes to AF [37].

HYPOXIA

Acute respiratory failure resulting from lung injury in patients with severe SARS-CoV-2 infection leads to the development of hypoxia. Hypoxia can activate anaerobic glycolysis by lowering intracellular pH, increasing the formation of oxygen free radicals, and increasing calcium levels in cardiomyocytes. This, in turn, may contribute to early and late depolarization, as well as cause temporary changes in the duration of the action potential. Hypoxia also causes an increase in the level of extracellular potassium, which lowers the depolarization threshold, accelerating electrical conductivity [38]. Airflow limitation and dynamic hyperinflation lead to increased pulmonary artery pressure and tricuspid regurgitation [39]. These patients with pulmonary hypertension are at significant risk of increased right atrial pressure and atrial distension, which is associated with a significant risk of developing AF [40].

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

Severe infections activate the sympathetic nervous system. There is an association between the activity of the sympathetic nervous system and the development of AF [41]. The sympathetic nervous system indirectly increases calcium influx into cardiomyocytes, which can lead to the generation of delayed post-depolarizations and trigger action potentials, thus increasing the likelihood of AF induction [42]. It has also demonstrated that inflammatory cytokines, especially IL-6, can induce hyperactivation of the sympathetic nervous system through central hypothalamus-mediated and peripheral pathways [43]. In some patients with COVID-19, anxiety can also cause hyperactivation of the sympathetic nervous system with subsequent development of arrhythmias [12].

Clinical observations show that increased parasympathetic activity also contributes to the onset of paroxysmal AF. Activation of the parasympathetic nervous system in COVID-19 is associated with control of the immune response and suppression of the "cytokine storm", which is realized through the inhibition of the production of tumor necrosis factor-α [44], IL-6, interleukin-1β [45]. The electrophysiological mechanisms of AF in this case mainly include lengthening of the atrial action potential, shortening of the refractory period due to the activation of potassium current. Cholinergic stimulation can also increase focal electrical activity in the area of the pulmonary veins [46].

CONCLUSION

Thus, acute COVID-19 infection may increase the risk of developing AF both in the acute period of the disease and in the long term due to multiple pathophysiological mechanisms. Potential mechanisms that may lead to arrhythmogenesis in patients with COVID-19 include hypoxia, reduced availability of ACE2 receptors, viral interactions with basigin and sialic acids, inflammatory cytokine storm, electrolyte and acid-base disturbances, autonomic nervous system dysfunction. Further study of these mechanisms will optimize the management of patients at high risk of developing AF with COVID-19.

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